(5) G. Zanati and M. E. Wolff, *J. Med. Chem.*, 14, 958 (1971).
(6) L. G. Hershberger, E. G. Shipley, and R. K. Meyer, *Proc. Soc. Exp. Biol. Med.*, 83, 175 (1953).
(7) M. E. Wolff and G. Zanati, *J. Med. Chem.*, 12, 629 (1969).

Synthesis and Antimalarial Activity of Anthracene Amino Alcohols

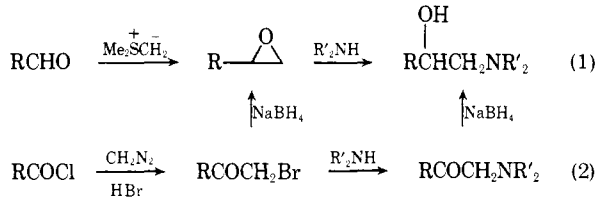
Eugene L. Stogryn

Government Research Laboratory, Esso Research and Engineering Company, Linden, New Jersey 07036.
Received November 29, 1973

In spite of the consistently high levels of antimalarial activity noted for phenanthrene amino alcohols,[1] the isomeric anthracene amino alcohols have been virtually ignored. The combination of negative biological data and synthetic difficulties afforded little incentive to conduct more than a cursory examination of this class of materials.[2] It was not until 1968 that the first example of an authentic "2 carbon" anthracene amino alcohol was described.[3] Subsequent evaluation noted that the 9-anthracene amino alcohols[4] prepared by Duncan were at least as active against *Plasmodium berghei* infected mice as the analogous 9-phenanthrene amino alcohols.† More recently Huffman[5] reported the synthesis of 10-chloro- and 10-bromo-9-anthracene amino alcohols, with the chlorine exerting the most favorable effect on antimalarial activity. Synthetic difficulties in this ring system apparently thwarted attempts to expand on their observation.

We describe herein our studies of anthracene amino alcohols aimed at a further delineation of activity dependence upon ring positions for (a) the basic amino alcohol side chain and (b) the pharmacophoric chlorine(s). These studies have been restricted to the "2 carbon" amino alcohol side chain terminating in either C_4 or C_7 hydrocarbon fragments because these structural features appear to be preferred in the highly active phenanthrene amino alcohols.[6]

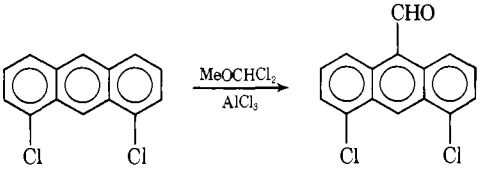
Chemistry. The Duncan[3] technique (sequence 1) for the introduction of the "2 carbon" amino alcohol side chain into aromatics offers obvious synthetic advantages over the more classical procedures. However, difficulties encountered in preparing the unknown chloro-substituted 1- and 2-anthraldehydes impeded its use for obtaining 1- and 2-anthracene amino alcohols. The synthesis of these isomers was realized *via* one of the routes which starts with acid chloride (sequence 2).



With the exception of 3-chloro-1-anthraquinonecarboxylic acid all the intermediate 1- and 2-anthraquinonecarboxylic acids employed in this study were obtained by the procedures detailed in the literature. The direct oxidation of 3-chloro-1-methylanthraquinone with 55% HNO_3 at 200° was found to be a more efficient route to this carboxylic acid than the involved scheme used by Kaimatsu.[7] Oxidation of this methyl group with various chromium or manganese oxidants was ineffectual. The classical Zn–NH_4OH reduction of anthraquinones to anthracenes converted the parent and substituted 1- and 2-anthraquinonecarboxylic acids to the corresponding anthroic acids. It is noteworthy that the integrity of the 4- and 8-position chlorine atoms was maintained during the Zn–NH_4OH reduction of 4,8-dichloro-1-anthraquinonecarboxylic acid. This reductive method is reported to result in the expulsion of chlorine from 4-chloro-1-anthraquinonecarboxylic acid.[8]

Standard techniques for the transformation of the carboxylic acid group to the α-bromomethyl keto function were applicable to the 1- and 2-anthroic acids. Conversion of the bromomethyl ketones to the amino alcohol function was realized through the intermediacy of anthracenyloxiranes and a subsequent ring opening with the appropriate amine, or *via* nucleophilic displacement of bromine by amine, followed by reduction of the resulting α-aminomethyl ketone. This latter sequence has been described as problematic with anthracenes‡ and other aryl systems,[9] because of instability of the α-aminomethyl aryl ketones. However, we have found it to be a perfectly viable route to "2 carbon" 1- and 2-anthracene amino alcohols. The amino alcohols prepared for this work are given in Table I.

Application of reaction sequence 2 to the preparation of 9-anthracene amino alcohol was precluded by the failure of 4,5- or 1,8-dichloro-9-anthroyl chloride to yield the α-bromomethyl ketone *via* the diazomethane route. However, two 9-anthracene amino alcohols, **11** and **12**, were obtained *via* reaction sequence 1. Synthesis of the requisite 4,5-dichloro-9-anthraldehyde was realized with the reagent Gross[10] described for the preparation of the parent 9-anthraldehyde.



This reagent also formylated 1,5-dichloroanthracene in the 9 position. However, all attempts to convert 1,5-dichloro-9-anthraldehyde to the corresponding anthracenyloxirane with various "methylene" transfer reagents were unrewarding. Huffman[5] similarly noted an inhibition of the methylene transfer reaction with certain halogenated 9-anthraldehydes.

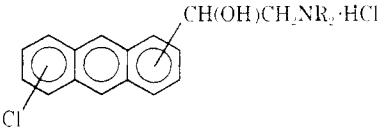
Biological Evaluation. All the anthracene amino alcohols listed in Table I, except **7**, were found to be active against *P. berghei* infected mice in the standard Rane[11] activity screen. Compound **12** was the most active material tested, effecting four cures per five test animals at a dosage of 80 mg/kg.

It appears that the structure–activity parameters known to be operative in carbocyclic amino alcohols such as phenanthrenes[2,6] and naphthalenes[2,6] are also significant to the activity of anthracene amino alcohols against *P. berghei*. For example, the levels of activity generally increase with the length of the terminal hydrocarbon fragment and chlorine(s) exerts prominent pharmacophoric effects on the anthracene amino alcohol activity. The lower activity level of the 2-anthracene amino alcohol **4** (compare **4** with

† 9-[1-Hydroxy-2-(di-*n*-heptylamino)ethyl]phenanthrene increased the survival time of the parasitized mice to 9.4 days at 160 mg/kg, 10.4 days at 320 mg/kg, and three curves at 640 mg/kg. Data supplied by R. E. Strube of WRAIR.

‡ 9-(ω-Bromoacetyl)anthracene is reported not to react with secondary amines. See ref 2d.

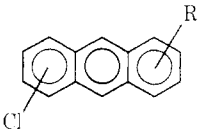
Table I



No.[a]	Ring position R[b]	Ring position Cl	Side chain	Method[c]	Mp, °C	Antimalarial act., ΔST, days[d] 40	80	160	320	640
1	C_4		1	A	167–167.5	0.3	0.3	0.3	2.1	6.4A
2	C_7		1	A	120.5–121	5.5	7.7A	10.3A	2C	3C
3	C_4		2	A (B)	123–124	0.3	0.3	0.5	3.9	10.7A
4	C_7		2	A	120.5–121	0.3	1.7	3.9	8.1A	13.7A
5	C_4	3	1	A	199–200	4.1	6.9A	10.7	1C	2C
6	C_7	3	1	A	153–154	6.9A	7.5A	1C	2C	
7	C_4	8	1	B	202–204	0.5			2.7	5.9
8	C_7	8	1	B	135–136.5	0.3			4.9	7.9A
9	C_4	4,8	1	B	238–241	4.1	11.3A	2C	5C	5C
10	C_7	4,8	1	B	184–187	4.1	7.7A	3C	5C	5C
11	C_4	4,5	9	C	221–223	10.3A	11.1A	13.3A	1C	2C
12	C_7	4,5	9	C	155–156.5	8.1A	4C	5C	5C	5C
13[e]	C_4		9			1.5	2.3	9.3A	12.1A	13.7A
14[e]	C_7		9			6.6A	6.8A	8.6A	2C	4C

[a]Recrystallization from benzene–heptane gave compounds **1–12** analyzing for C, H, and Cl within ±0.4% of the theoretical values. [b]C_4 and C_7 are straight-chain hydrocarbon moieties. [c]Synthetic methods are detailed in the Experimental Section. [d]Mice were treated 3 days postinfection sc with a single dose of the compound being screened. The change in survival time (ΔST) is an indication of activity against *P. berghei*. ΔST values > 6.0 days are classified as active (A). Survival of >60 days are considered as cures (C). Testing was performed by Dr. L. Rane and coworkers, Malaria Screen Laboratory, University of Miami, Fla. [e]Test data presented by R. E. Strube.[4]

Table II



Ring position Cl	Ring position R	CO_2H[a] Mp, °C	CO_2H[a] Analyses[c]	$COCH_2Br$[b] Mp, °C	$COCH_2Br$[b] Analyses[c]	Mp, °C	Analyses[c]
	1	248–249[d,e]		63[d]	C, H	101–101.5	C, H
	2	285[e]		153–153.5	C, H	204.5–206.5	C, H
3	1	275–276	C, H, Cl	121–122	C, H	96–97	C; H[f]
8	1	267–268[g]		147–149	C, H		
4,8	1	291[h]	C, H, Cl	145.5–146	C, H		
4,5	9					151–152	C, H

[a]Recrystallized from HOAc. [b]Recrystallized from heptane. [c]See footnote *a* in Table I. [d]Recrystallized from MeOH. [e]C. Graebe and S. Blumenfeld, *Ber.*, **30,** 1115 (1912). [f]H: calcd, 4.35; found, 4.79. [g]Reference 12. [h]Recrystallized from EtOH–H_2O.

2 and **14**) is consonant with the effect of side-chain position on activity in naphthalenes; *i.e.*, 1-naphthalene amino alcohols are more active than comparable 2 isomers.

Experimental Section

Anthracene Amino Alcohols. The compounds listed in Table I were prepared by one of the following methods. Where the synthetic schemes require anthroic acids they were prepared by a Zn–NH_4OH reduction of the appropriate anthraquinonecarboxylic acids as detailed by Golden.[12] The anthroic acids and other intermediates used in the various methods are listed in Table II.

Method A. 2-Anthroyl chloride in THF solvent was converted to the corresponding α-bromomethyl ketone in 76% yield *via* a standard CH_2N_2–HBr procedure. To a solution of 0.5 mol of $NaBH_4$ in 45 ml of EtOH was added 3.1 g of 2-(ω-bromoacetyl)-anthracene in 40 ml of THF. After 15 min at 20–25°, 2.07 g of NaOH in 5.2 ml of H_2O was added. The reaction was stirred for 1 hr and poured into a large volume of H_2O, and the precipitated 2-anthracenyloxirane was filtered and recrystallized. The oxirane (0.0104 mol) and a 9 molar excess of di-*n*-heptylamine in 13 ml of dry DMF were heated at 100–105° for 16 hr. Removal of DMF and excess amine, under reduced pressure, left a viscous residue which was dissolved in Et_2O and treated with gaseous HCl. The precipitated product was filtered and recrystallized.

Method B. To a solution of 2 g of 1-(ω-bromoacetyl)-4,8-dichloroanthracene in 25 ml of THF was added 2.9 g of di-*n*-heptylamine in 5 ml of THF at ambient temperature. After 1 hr the THF was evaporated; the residue was triturated with pentane and filtered. The pentane residue was dissolved in EtOH–THF and reacted with 0.42 g of $NaBH_4$ for 1.5 hr. Concentration of the reaction mixture, dilution with H_2O, extraction with Et_2O, and acidification with gaseous HCl yielded the anthracene amino alcohol hydrochloride salt.

Method C. Preparation of 9-(4,5-dichloroanthracenyl)oxirane from the corresponding anthraldehyde was realized by the procedure detailed by Duncan.[3] Conversion of the oxirane to the amino alcohol followed method A.

3-Chloro-1-anthraquinonecarboxylic Acid. A mixture of 4 g of 3-chloro-1-methylanthraquinone[7] and 6 ml of 55% HNO_3 was heated in a glass autoclave at 200–210° for 6 hr. The cooled reaction mixture was diluted with H_2O, filtered, and H_2O washed. Extraction of the filter cake with hot, dilute NH_4OH, acidification, and recrystallization from HOAc gave yellow crystals, mp 282–285° (lit.[7] 286–287°).

4,5-Dichloro-9-anthraldehyde. To a solution of 26.4 g of 1,8-dichloroanthracene and 26.6 g of $AlCl_3$ in 750 ml of CH_2Cl_2 was added 14.4 g of α,α-dichloromethyl methyl ether in 10 ml of CH_2Cl_2. After 1 hr at ambient temperature, the reaction was poured into cold dilute HCl, extracted with PhH, and chromatographed through silica gel. Benzene eluate contained unreacted

1,8-dichloroanthracene. The 9-anthraldehyde was eluted from the column with THF: yield 9 g; mp 224–226° (THF). *Anal.* ($C_{15}H_8Cl_2O$) C, H.

1,5-Dichloro-9-anthraldehyde. Formylation of 34.4 g of 1,5-dichloroanthracene with 20.2 g of α,α-dichloromethyl methyl ether as detailed in the preceding preparation yielded 3 g of the titled compound, mp 188–190° (PhH–heptane). *Anal.* ($C_{15}H_8Cl_2O$) C, H, Cl.

Acknowledgment. The author wishes to express gratitude to Dr. R. E. Strube for the encouragement of this work and to the U. S. Army Medicinal Research and Development Command for their financial support. This work was performed under Contract No. DADA17-71-C-1038 and is Contribution No. 1217 from the Army Research Program on Malaria.

References

(1) (a) P. Chien, D. J. McCaustland, W. H. Burton, and C. C. Cheng, *J. Med. Chem.*, 15, 28 (1972); (b) W. T. Colwell, V. Brown, P. Christie, J. Lange, C. Reece, K. Yamamoto, and D. W. Henry, *ibid.*, 15, 771 (1972); (c) E. A. Nodiff, A. J. Saggiomo, M. Shimbo, E. H. Chen, H. Otomasu, Y. Kondo, T. Kikuchi, B. L. Verma, S. Matsuura, K. Tanabe, M. P. Tyagi, and S. Morosawa, *ibid.*, 15, 775 (1972).

(2) (a) F. Y. Wiselogle, "A Survey of Antmalarial Drugs: 1941–1945," J. W. Edwards, Ed., Ann Arbor, Mich., 1946; (b) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, "Survey of Antimalarial Agents," Public Health Monograph No. 9, Washington, D. C., 1953, p 182; (c) E. L. May and E. Mossettig, *J. Org. Chem.*, 11, 353 (1946); (d) E. L. May and E. Mossettig, *J. Amer. Chem. Soc.*, 70, 686 (1948).

(3) W. G. Duncan, W. T. Colwell, C. R. Scott, and D. W. Henry, *J. Med. Chem.*, 11, 1221 (1968).

(4) R. E. Strube, Aminoalcohol Antimalarial Conference, Walter Reed Army Institute of Research, Washington, D. C., May 1969.

(5) J. T. Traxler, E. P. Lira, and C. W. Huffman, *J. Med. Chem.*, 15, 861 (1972).

(6) See ref 2 and E. A. Steck, "The Chemotherapy of Protozoan Diseases," Vol. III, Division of Medicinal Chemistry, Walter Reed Army Institute of Research, 1971, p 23.65.

(7) S. Kaimatsu, I. Hiramo, and T. Tanabe, *Chem. Abstr.*, 23, 4696 (1929).

(8) O. Fischer and A. Sapper, *J. Prakt. Chem.*, [2] 83, 201 (1911).

(9) T. L. Jacobs, S. Winstein, J. Ralls, J. H. Robson, R. B. Henderson, R. Akawie, W. Florsheim, D. Seymour, and C. Seil, *J. Org. Chem.*, 11, 21 (1946); (b) K. N. Campbell and J. F. Kerwin, *J. Amer. Chem. Soc.*, 68, 1837 (1946); (c) D. R. V. Golding and W. H. McNeely, *ibid.*, 68, 1847 (1946).

(10) H. Gross and J. Rusche, *Chem. Ber.*, 99, 2625 (1966).

(11) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, 10, 431 (1967).

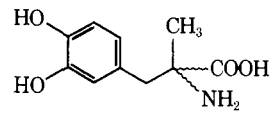
(12) R. Golden and L. M. Stock, *J. Amer. Chem. Soc.*, 94, 3080 (1972).

Rigid Amino Acids Related to α-Methyldopa

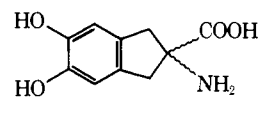
Joseph G. Cannon,* John P. O'Donnell, John P. Rosazza, and Charles R. Hoppin

Division of Medicinal Chemistry and Natural Products, College of Pharmacy, The University of Iowa, Iowa City, Iowa 52242.
Received December 17, 1973

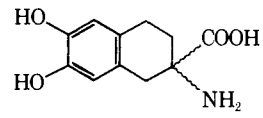
The antihypertensive activity of α-methyldopa (1) has prompted numerous workers to incorporate the salient features of this molecule into a rigid framework. Taylor, *et al.*,[1] prepared an indan derivative 2 and its dimethyl ether, both of which were inactive in an *in vivo* screen for hypotensive activity. The compounds were likewise inactive in *in vitro* screens against Dopa decarboxylase, and it was concluded that the rigidity and symmetry incorporated into this molecule (compared to α-methyldopa) was the possible cause of the biological inactivity. Rastogi, *et al.*,[2] prepared an analogous tetralin amino acid 3 and found no hypotensive effect and no *in vitro* inhibition of Dopa decarboxylase. Neither the Taylor nor the Rastogi group described the Dopa decarboxylase inhibition test which was employed.



1

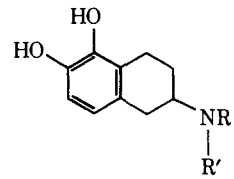


2

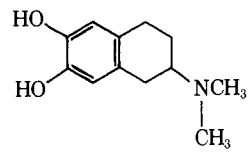


3

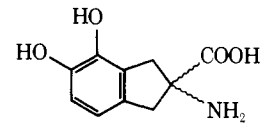
The dramatically high order and wide spectrum of biological effects produced by 2-dimethylamino-5,6-dihydroxytetralin (4),[3,4] as compared with the 6,7-dihydroxy system 5,† suggested that molecular rigidity *per se* might not be the critical parameter for biological effect but that the arrangement of the OH functions on the aromatic ring is critical.



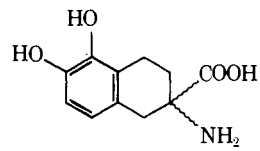
4, R = R′ = Me
9, R = R′ = H



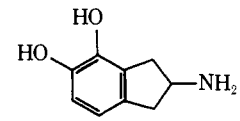
5



6



7



8

It was speculated that the OH group disposition in 2 and 3 might be detrimental to maximal α-methyldopa-like effects, and accordingly the indan and tetralin systems 6 and 7 were selected for preparation and biological study. These systems are, like 2 and 3, rigid analogs of α-methyldopa, but they represent different frozen rotamers of it. Attention was limited in the present work to *in vitro* effects of the amino acids on Dopa decarboxylase.

Compounds 6 and 7 were prepared from the corresponding ketones by literature modifications of the Strecker reaction. Preparation of the amines 8 and 9 (which are decarboxylation products of 6 and 7) has been described in prior communications;[3,5] however, in the present work, the dimethyl ether of 9 was synthesized from the appropriate β-tetralone by conversion to its *O*-methyl oxime and reduction of this with diborane. Overall, this sequence represents a marked improvement over the literature one. Spectral (ir and nmr) data on all compounds

† J. P. Long, University of Iowa, unpublished data.